UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,433	08/26/2003	Jerome S. Schultz	03-016	5277

7590 04/07/2006

Parrish Law Offices
Suite 200
615 Washington Road
Pittsburgh, PA 15228

EXAMINER	
TSAY, MARSHA M	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,433	SCHULTZ ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received January 25, 2006. Claims 10-11 are canceled. Claims 1-9, 12-17 are pending and currently under examination.

Priority: The priority date is August 26, 2002.

Withdrawal of Objections and Rejections

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US 5998204) is withdrawn.

Maintenance of/New Objections and Rejections

Claims 1-2, 4, 7, are objected to because of the following informalities: the subclaims are not correctly alphabetized. For instance, claim 1 has subclaims a), d) and e), which should be corrected to a), b), and c). Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-9, 12-13, 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 15 are currently amended to recite analytes are reversibly glucose bound. The claim is indefinite because it is unclear how an analyte is reversibly

"glucose" bound. It is unclear if Applicants are referring to glucose as being the analyte. Further clarification is required.

Claims 2-3 are included in this rejection because they are dependent on claim 1.

Claims 4-5, 8-9, 16-17 recite EBFP, YFP and GFP. It is acknowledged that the specification provides a definition for EBFP, YFP, and GFP; however, Applicants should provide a definition of what EBFP is in order to clarify the claim and clearly define what is being claimed.

Claims 6, 12-13 are included in this rejection because they are dependent on the above claims.

In their response, Applicants assert a cross-reference to the acronyms are disclosed in the specification. Examiner already acknowledged that the instant specification provides a reference to the EBFP, YFP, and GFP acronyms in the August 25, 2005 Office action. However, the issue is that the instant claims should also incorporate this definition into the claims, such that claim 4(c) recites "said second moiety is Enhanced Blue Fluorescent Protein (EBFP)...". Similar corrections are requested for claims 5-6, 8-13, and 16-17.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected again under 35 U.S.C. 102(b) as being anticipated by Lakowicz et al. (US 6197534). Lakowicz et al. teach biosensors for detecting analytes, such as glucose, by genetically engineering a protein for site-specific positioning of allosteric signal transducing molecules. In example 4, Lakowicz et al. teach a specific glucose sensor comprising a GGBP (glucose/galactose binding protein) fusion protein with fluorophores at both the C-terminal and N-terminal positions (col. 9, lines 44-46; claim 1, 2). Lakowicz disclose the protein is an *E.coli* glucose/galactose protein (GGBP) (col. 4, lines 21-22). In Figure 18, Lakowicz et al. teach a donor molecule Green Fluorescent Protein (GFP) is attached at the C terminal and an acceptor molecule Blue Fluorescent Protein (BFP) is attached at the N-terminal of GGBP (col. 9, lines 47-49; claim 1, 2). The donor and acceptor molecules or moieties are positioned on GGBP such that binding of glucose causes a conformational change to the GGBP (col. 9; lines 54-56; claim 1, 2). The conformational change brings the donor and acceptor fluorophores closer together so that emission from the donor fluorophore GFP is quenched by absorbance by the acceptor fluorophore BFP (col. 9, lines 55-60; claim 1-3). Lakowicz et al. teach the spectral changes of GGBP can be measured with low cost devices, such as laser diodes, light emitting diodes, or electroluminescence light sources (col. 6, lines 36-40; claims 1-3).

In their response, Applicants assert claims 1, 7, and 15 have been amended in order to narrow the scope of each independent claim. Specifically, these novel elements include (i) a reversibly glucose bound moiety; whose second and third

moieties interact to produce a (ii) fluorescent change, that (iii) is optically detectable by external means; when (iv) in subcutaneous contact with a fluid of interest. Claim 1 currently comprises elements (i), (ii), and (iii), which as explained in the 102(b) rejection above are anticipated by Lakowicz et al.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7, 9, 14 are rejected again under 35 U.S.C. 103(a) as being unpatentable over Lakowicz et al. (US 6197534). Lakowicz et al. teach biosensors for detecting analytes, such as glucose, by genetically engineering a protein for site-specific positioning of allosteric signal transducing molecules. Lakowicz et al. disclose Glucose/Galactose binding protein of *Escherichia coli* (GGBP) is employed as a sensing molecule and fused with fluorophore molecules bound to each side and where conformational changes of GGBP upon glucose binding can shift the positions of the fluorophores and fluorescent energy transfers between the donor and acceptor fluorophore molecules (col. 5, lines 55-66). Lakowicz et al. teach an actual working example of a GGBP (glucose/galactose binding protein) fusion protein with GFP attached at the C terminal and BFP is attached at the N-terminal (col. 9, lines 44-50). Lakowicz disclose the protein is an *E.coli* glucose/galactose protein (GGBP) (col. 4, lines 21-22). Lakowicz et al. also disclose the glucose sensors may be used to

measure glucose concentrations present in extracted interstitial fluid, obtained from perturbing the outer skin layer (col. 6, lines 9-12). For a GGBP-based sensor, the motion of the two domains of the proteins is needed and should occur in polymeric supports (col. 6, lines 25-26). When labeled with suitable fluorophores, spectral changes are observed wherein glucose binding is detected by changes in emission intensity or energy transfer efficiencies. Useful spectral shifts may also be observed with fluorophore-labeled fusion proteins created from GGBP or its mutants (col. 6, lines 26-35). Lakowicz et al. disclose the spectral changes shown for GGBP can be measured with low cost devices such as laser diodes, light emitting diodes, or electroluminescence light sources (col. 6, lines 36-40). The sensor may also use a variety of sensing molecules, with different fluorescent labels (col. 6, lines 44-45).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to construct a biosensing system for glucose comprising an biosensor element such as a fusion protein comprising glucose binding domain fused with fluorophores such as GFP and BFP, at the N-terminal and C-terminal ends of the protein (claim 1-3, 7a), wherein the protein is placed on a surface such as a polymeric support (claim 7a), wherein the glucose sensor is placed in subcutaneous interstitial fluid to measure the concentration of glucose by an electroluminescence light source device (claim 7b, 7c, 14) because Lakowicz et al. disclose a glucose sensor comprising a fusion protein of GGBP with GFP and BFP attached at the N-terminal and C-terminal ends and where the glucose sensor can be employed for monitoring of glucose concentration in interstitial fluid obtained from perturbing the skin layer.

In their response, Applicants assert claims 1, 7, and 15 have been amended in order to narrow the scope of each independent claim. Specifically, these novel elements include (i) a reversibly glucose bound moiety; whose second and third moieties interact to produce a (ii) fluorescent change, that (iii) is optically detectable by external means; when (iv) in subcutaneous contact with a fluid of interest. Claims 7 and 15 differ from claim 1 with the added element of the biosensing system being in subcutaneous contact with a fluid of interest. While Lakowicz et al. do not specifically use the term "subcutaneous" contact to describe the placement of their biosensing system, Lakowicz et al. do disclose that GGBP may be used to measure glucose concentration in interstitial fluid that is obtained from perturbing skin (col. 6, lines 10-15). One of ordinary skill in the art would recognize that the biosensing system of Lakowicz et al. would still detect glucose by fluorescent change whether placed in extracted interstitial fluid from the skin or placed in "subcutaneous" contact with the fluid. The rejection of the claims are still maintained.

Claims 1-3, 5, 9 are rejected again under 35 U.S.C. 103(a) as being unpatentable over Lakowicz et al. (US 6197534) in view of Fehr et al. (2002 PNAS 99(15): 9846-9851). The teachings of Lakowicz et al. are outlined above. Lakowicz et al. do not teach the use of YFP (yellow fluorescent protein) in a biosensor.

Fehr et al. teach the visualization of maltose uptake by fluorescent nanosensors. Fehr et al. teach the construction of a fluorescent indicator protein wherein a truncated

male PCR product encoding mature maltose-binding protein (MBP) was fused between a gene encoding an enhanced cyan fluorescent protein (ECFP) and a gene encoding an enhanced yellow fluorescent protein (EYFP) (p. 9846, experimental). Fehr et al. disclose ECFP and EYFP are green fluorescent protein (GFP) variants.

It would also have been obvious to a person having ordinary skill in the art to construct a fusion protein comprising a glucose binding domain with fluorophore molecules, such as the combination of YFP and GFP (claim 5) and utilize this sensor element in a biosensing system (claim 9) because Lakowicz et al. teach and suggest that suitable fluorophores can be used in the construction of a glucose sensor fusion protein and used in a biosensing system while Fehr et al. teach the use of YFP and CFP as fluorophore molecules in a biosensor for detecting an analogous sugar molecule.

Claim 15 is rejected again under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. (US 5998204) in view of Lakowicz et al. (US 6197534). Tsien et al. teach fluorescent indicators including a binding protein moiety, a donor fluorescent protein moiety, and an acceptor fluorescent protein moiety can be produced as fusion proteins by recombinant DNA technology. Tsien et al. teach a fluorescent indicator for Ca^{2+} was produced by sandwiching CaM-M13 fusion between a blue and a green GFP mutant and cloned into pRSETB (col. 22, lines 28-31). The fluorescent indicator was efficiently expressed and folded in bacteria and increased its ratio of UV-excited 510 nm to 445

nm emissions by 70% upon binding Ca^{2+} (Fig. 3) (col. 22, lines 62-65). Tsien et al. do not teach the expression of fluorescent indicators for measuring glucose.

The teachings of Lakowicz et al. are outlined above. Lakowicz et al. do not teach an expression vector coding for the glucose sensor protein and wherein the method of measuring glucose is measured within cells.

It would have been obvious to a person having ordinary skill in the art to non-invasively measure glucose concentration within a cell by introducing a plasmid/expression vector encoding a glucose binding domain fused with fluorophore molecules at the N-terminal and C-terminal ends into a cell, expressing the fluorescent indicator protein, and measuring the spectral changes upon the binding of an analyte, in this instance a glucose molecule (claim 15), because Lakowicz et al. teach the detection of glucose through a fluorescence indicator protein and Tsien et al. use the same technology and teach the successful expression of a fluorescent indicator protein that measures an analyte within cells.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen Cochrane Carlson Ph.D

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

March 24, 2006